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GREENBLUM & BERNSTEIN, P.L.C. 1950 ROLAND CLARKE PLACE RESTON, VA 20191				KAPUSHOC, STEPHEN THOMAS
ART UNIT		PAPER NUMBER		
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

gbpatent@gbpatent.com  
pto@gbpatent.com

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/568,695	TANAKA ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 07 October 2008.  
 2a) This action is FINAL.                    2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-13 is/are pending in the application.  
 4a) Of the above claim(s) 5-13 is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1-4 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on 21 November 2006 is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____ .                                    |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>1/18/08; 9/15/08</u> .  | 6) <input type="checkbox"/> Other: _____ .                        |

**DETAILED ACTION**

Claims 1-13 are pending.

Claims 5-13 are withdrawn from examination as detailed below.

Claims 1-4 are examined on the merits.

***Election/Restrictions***

1. Applicant's election with traverse of the invention of Group 1, claims 1-4, in the reply filed on 10/07/2008 is acknowledged. The traversal is on the ground(s) that there is a special technical feature which defines a contribution over the cited prior art reference of GenBank Accession AL022215. Applicants have not indicated what particular special technical feature (a feature not described by any prior art and required of all the claims) provides unity of invention for the different Groups. Applicants have further argued that there would not be a burden in searching and examining multiple groups of inventions. This is not found persuasive because the claims of the instant application are filed in a 371 national stage application of a PCT application, and thus the relevant issue for the separation of the different groups of inventions is unity of invention requiring a special technical feature, not search burden.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 5-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/07/2008.

***Claim Rejections - 35 USC § 101***

3. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 1-4 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The rejected claims are drawn to methods judging inflammatory diseases. The claimed invention falls within an enumerated statutory category, namely a process.

The rejected claims are drawn to methods for judging comprising the single step of detecting a polymorphism in the galectin-2 gene.

In re Bilski No. 2007-1130 (Fed Cir. October 30, 2008) characterizes its machine-transformation test as "the governing test for determining patent eligibility of a process under section 101." Under this test, a process claim is patent-eligible if (and, as applied in Bilski, only if): "(1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing." The claims are not directed to patent-eligible subject matter since they are not tied to any particular machine or apparatus and they do not require any particular article to be transformed into another state or thing.

None of the rejected claims requires the transformation of an article or physical object to a different state. For example, relevant to the rejected claims, one could detect the required polymorphism merely by consulting a digital record in an electronic

database of nucleic acid sequence information previously derived during a genome sequencing project. Additionally, there is no result tied to the physical world. There is no required transformation of an article or physical object to a different state.

Transformation of data is not considered a physical transformation.

As clearly noted in *In re Comiskey No. 2006-1286* (Fed. Cir. Sept. 20, 2007), "the Supreme Court has reviewed process patents reciting algorithms or abstract concepts in claims directed to industrial processes. In that context, the Supreme Court has held that a claim reciting an algorithm or abstract idea can state statutory subject matter only if, as employed in the process, it is embodied in, operates on, transforms, or otherwise involves another class of statutory subject matter, i.e., a machine, manufacture, or composition of matter. 35 U.S.C. § 101." Regarding *In re Comiskey*, the USPTO noted, "[t]he Supreme Court has recognized only two instances in which such a method may qualify as a section 101 process: when the process 'either [1] was tied to a particular apparatus or [2] operated to change materials to a 'different state or thing.'" (quoting *Flook*, 2006-1286 17 437 U.S. at 588 n.9). In *Diehr*, the Supreme Court confirmed that a process claim reciting an algorithm could state statutory subject matter if it: (1) is tied to a machine or (2) creates or involves a composition of matter or manufacture. 450 U.S. at 184. There, in the context of a process claim for curing rubber that recited an algorithm, the Court concluded that "[t]ransformation and reduction of an article 'to a different state or thing' is the clue to the patentability of a process claim that does not include particular machines." *Id.* (quoting *Benson*, 409 U.S. at 70);<sup>13</sup> see also *In re*

Schrader, 22 F.3d 290, 295 (Fed. Cir. 1994) (holding when a claim does not invoke a machine, "§ 101 requires some kind of transformation or reduction of subject matter").

Finally, the Comisky opinion states that mental processes- or processes of human thinking- standing alone are not patentable even if they have practical application. The Supreme Court has stated that "[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." Benson, 409 U.S. at 67. In Flook the patentee argued that his claims did not seek to patent an abstract idea (an algorithm) because they were limited to a practical application of that idea-updating "alarm limits" for catalytic chemical conversion of hydrocarbons. 437 U.S. at 586, 589-90. The Court rejected the notion that mere recitation of a practical application of an abstract idea makes it patentable, concluding that "[a] competent draftsman could attach some form of post-solution activity to almost any mathematical formula." Id. at 590.

In the case of the instant claims, there is no recitation of producing a real-word result that is tied to a machine or apparatus or causes a transformation of an article. In other words, the outcomes of the rejected methods lack a tie to the machine or apparatus and lack a physical transformation. Thus the claims are rejected as encompassing non-statutory subject matter.

The claims may be drawn to statutory subject matter if the methods are amended to specifically require the steps of, for example: (a) obtaining a biological sample from a subject, said sample comprising nucleic acids of the subject; (b) detecting in said

nucleic acids the presence a C at position 3279 of SEQ ID NO: 1; and (c) correlating the presence of a C at position 3279 of SEQ ID NO: 1 in said nucleic acids with an increased risk of myocardial infarction in the subject.

***Claim Rejections - 35 USC § 112 2<sup>nd</sup> ¶ - Indefiniteness***

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4 are unclear over the stated purpose of the claimed methods as 'for judging inflammatory diseases' as recited in the preamble of independent claim 1. The rejected methods comprise only the single method step of detecting a polymorphism. However the single step of detecting a polymorphism does not render any judgment. The claims may be made more clear if amended to require a step of correlating detected nucleotide content with a diagnosis of inflammatory disease risk, or if amended to recite a clause specifying wherein the presence of particular detected nucleotide content is indicative of inflammatory disease risk.

Claims 1-4 are unclear over the recitation of the limitation of 'judging inflammatory disease', where the claim does not recite any requirements of a judgment. The term 'judging' is not an art recognized term with regard to the analysis of any particular qualities of any inflammatory disease. As such the metes and bounds of the

claim are unclear. It is unclear what conclusion the artisan practicing the invention is required to make in a method 'for judging inflammatory diseases'.

Claim 3 is unclear over recitation of the phrase 'detecting the C/T polymorphism at nucleotide 3279 in the nucleotide sequence of intron 1 of the galectin-2 gene as shown in SEQ ID NO: 1'. Because a polymorphism is variable nucleotide content in a nucleic acid population, it is unclear how the 'C/T polymorphism' is detected in a nucleic acid in the claimed method. Further, because of the language of the claim, it is unclear if the claim requires detection of specific nucleotide content in the recited position of some sequence of intron 1, or the particular sequence of SEQ ID NO: 1. For these reasons the metes and bound of the claim are unclear. The claim may be made more clear if amended to require detection of particular nucleotide content within a specific sequence context, for example: detecting a C at the position in the nucleotide sequence of intron 1 of the galectin-2 gene corresponding to position 3279 of SEQ ID NO: 1.

***Claim Rejections - 35 USC § 112 1st¶ - Written Description***

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants are directed to the Written Description Training Materials revised March 25, 2008, available online at [www.uspto.gov/web/menu/written.pdf](http://www.uspto.gov/web/menu/written.pdf).

The rejection of claims for lack of adequate written description is relevant the requirement of the claims, as encompassing any ‘gene polymorphism in the galectin-2 gene’, or ‘the C/T polymorphism at nucleotide 3279 in the nucleotide sequence of intron 1 of the galectin-2 gene as shown in SEQ ID NO: 1’ (as recited in the claims) with the required functionality of rendering a judgment regarding an inflammatory disease. In the instant case the specification does not provide the skilled artisan with an adequate written description of a the particular mutation within the generic breadth of the claims with the required diagnostic functionality, nor an adequate structural limitation of the particular content required by the recitation of ‘nucleotide 3279 in the nucleotide sequence of intron 1 of the galectin-2 gene as shown in SEQ ID NO: 1’ (because of the indefiniteness issues associated with the language, as detailed earlier in this Office Action) with the required diagnostic functionality.

The rejected claims are generic with regard to the polymorphisms in the galectin-2 gene that are used in the claimed method for rendering a judgment regarding an inflammatory disease. Thus when the claims are analyzed in light of the specification, the claims encompass a large genus of nucleotide contents in a variety of sequence contexts. However the specification does not provide any strucutre:function correlation that would allow the skilled artisan to *a priori* identify the required functionality of any

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generically encompassed SNP. For example, the skilled artisan, given the teachings of the specification and the prior art, does not now how the detection of a G at position 60 of SEQ ID NO: 3 would effect any judgment of any inflammatory disease.

The lack of limiting nucleotide sequence context and content in view of the recitation of a polymorphism with a functional requirement in a disease analysis method is particularly relevant in analysis of polymorphisms in the galectin-2 gene. For example, the GeneCards reference for the galectin-2 gene indicates that there are at least 104 single nucleotide polymorphisms in the Galectin-2 gene, where there is no indication in the specification or the prior art as to which SNPs will have any particular functionality in judging inflammatory diseases.

Relevant to the lack of particular structural limitations in the rejected claims, MPEP 2163 states:

The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art.

In the instant claims, the detection of particular nucleotide content at a particular position, and the correlative association of that content with a judgment of an inflammatory disease is critical to the claimed invention. However, given the particular recitations in the claims and the lack of limiting structural requirements of the required mutation in the specification, one of skill in the art can not *a priori* identify the required mutation required of the claims which have the particular diagnostic functionality.

In conclusion, having considered the breadth of the claims, and the particular teachings of the instant specification, and the teachings of the prior art, the specification, while providing a written description of methods requiring:

detecting a C at the position in the nucleotide sequence of intron 1 of the galectin-2 gene corresponding to position 3279 of SEQ ID NO: 1.

does not provide an adequate written description of the broadly claimed subject matter.

***Claim Rejections - 35 USC § 112 1<sup>st</sup> ¶ - Enablement***

8. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

**Nature of the invention and breadth of the claims**

The instant claims are drawn to methods for judging inflammatory diseases.

The claims broadly encompass the detection of any generic polymorphism in the galectin-2 gene.

The claims encompass any judgment of any inflammatory disease.

The claims encompass the analysis of any subject organism.

The claims thus require knowledge of a some correlative association between the broadly claimed nucleotide content of the galectin-2 gene and any judgment of any inflammatory disease.

**Direction provided by the specification and working example**

The specification provides an example of the identification of a polymorphism in the human galectin-2 gene, where the polymorphic content is either a C or a T at position 3279 of SEQ ID NO: 1 (p.6-7).

The specification teaches (p.16; p.20-21), the analysis of the polymorphisms in case and control populations to study the association of the SNP content with the presence of myocardial infarction (MI). The specification asserts that the presence of the TT genotype at the position in both alleles of the galectin-2 gene is indicative of a decreased risk of MI (p.20).

The specification does not provide any examples of the analysis of any other particular polymorphic positions, or the analysis of any inflammatory diseases other than MI, or any non-human analyses. There is no validation analysis of any additional population other than the subjects as presented in Table 1 on page 21 of the specification.

#### **State of the art, level of skill in the art, and level of unpredictability**

While the state of the art with regard to the detection of any particular nucleotide sequence is high, the unpredictability with regard to the association of any particular sequence with a particular phenotype, or the identification of any nucleotide sequence having a particular functionality, is even higher. The unpredictability is demonstrated by the prior art and the post-filing art.

The claims of the instant application generically encompass any mutation in the galectin-2 gene of any subject organism. Because the methods of the claims are not limited to any particular nucleotide sequence content, it is relevant to point out the

unpredictability in associating any sequence content with a particular phenotype. For example, Hacker et al (1997) teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (pages 623-627).

Because the claims encompass diagnostic methods in any subject organism, it is relevant to point out the unpredictability in extrapolating the presence of polymorphic nucleotide content, or its association with any phenotype, from one animal to any other different animal. Such unpredictability in interspecies extrapolation is addressed by Juppner (1995), which teaches that despite significant structural conservation, rat, opossum, and human PTH/PTHrP receptor homologs display distinct functional characteristics (Abstract; pp.39S-40S).

And while the claims are generically drawn to c methods comprising detecting any polymorphism, while the instant specification teaches only the analysis of a particular SNP, it is relevant to point out the unpredictable nature of any mutation association study. As evidence of the unpredictability of gene association studies, Lucentini (2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in

the gene association studies (middle column, 1st complete paragraph). Additionally, Hegele (2002) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

The unpredictability as generally described by Lucentini and by Hegele, as cited above, is particularly relevant considering the teachings of the post-filing art. For example, the post filing-art teaches the analysis of the same SNP in the galectin-2 gene and a lack of association with MI. Mangino et al (2007) teach that the SNP rs7291467 (the same SNP of the instant application) is not associated with MI in a Caucasian population (p.114 left col.). Similarly, Sedlacek et al (2007) teaches (p.1000, Table 3) that there is no significant association between the same SNP and MI in two German populations. Finally, Kimura et al teaches that there was no association of the SNP with MI in a Japanese population or a Korean population (p.267, left col.; Table 3). It is thus unpredictable as to whether or not the asserted association of the instant specification would in fact reliably or robustly be reproduced in any other different population.

**Quantity of experimentation required**

A large and prohibitive amount of experimentation would have to be performed in order to make and use the claimed invention. Such experimentation would include large case:control studies in populations of any subject organism to demonstrate a robust and reliable association of different nucleotides contents with any inflammatory disease. Even for the particular SNP disclosed in the specification, one would have to perform large case:control studies to establish whether or not the asserted associations are reliable and robust in any subject population of interest. Such experimentation would be extensive. Even if one were to carry out such experimentation, there is no assurance that a reliable and consistent association of genetic content, consonant with the breadth of the claims, with any inflammatory disease or even MI would be identified.

### **Conclusion**

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the guidance provided by the applicant and the specific examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention.

### ***Conclusion***

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Stephen Kapushoc/

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